

We claim:

1. A method of differentiating progenitor cells, comprising the steps of:

5 (a) contacting said progenitor cells with a differentiating agent; and

(b) introducing into said progenitor cells a nucleic acid molecule encoding a MEF2 polypeptide or an active  
10 fragment thereof,

thereby differentiating said progenitor cells to produce a cell population containing protected neuronal cells.

2. The method of claim 1, wherein said MEF2  
15 polypeptide is human MEF2C, or an active fragment thereof.

3. The method of claim 1, wherein said MEF2 polypeptide is constitutively active.

4. The method of claim 3, wherein said  
20 constitutively active MEF2 polypeptide is a MEF2/VP16 fusion protein.

5. The method of claim 3, wherein said constitutively active MEF2 polypeptide contains one or more serine/threonine to aspartic acid/glutamic acid  
25 substitutions in the MEF2 transactivation domain.

6. The method of claim 1 or claim 3, further comprising inhibiting caspase activity in said progenitor cells.

7. The method of claim 1, wherein said progenitor  
5 cells are human stem cells.

8. The method of claim 1, wherein said progenitor cells are embryonic stem cells.

9. The method of claim 8, wherein said embryonic stem cells are human embryonic stem cells.

10 10. The method of claim 1, wherein said progenitor cells are hematopoietic progenitor cells.

11. The method of claim 10, wherein said hematopoietic progenitor cells are human hematopoietic progenitor cells.

15 12. The method of claim 1, further comprising selecting CD133-positive human progenitor cells.

13. The method of claim 1, further comprising selecting CD133-positive/CD34-positive human progenitor cells.

20 14. The method of claim 1, further comprising selecting CD133-positive/CD34-negative human progenitor cells.

15. The method of claim 1, further comprising selecting CD133-positive/CD34-negative/CD45-negative human progenitor cells.

16. The method of claim 1, further comprising  
5 selecting CD34-negative/CD38-negative/Lin-negative human progenitor cells.

17. The method of claim 1, further comprising selecting CD34-positive/CD38-negative/Lin-negative/Thy-1-negative human progenitor cells.

10 18. The method of claim 1, wherein said differentiating agent is retinoic acid.

19. The method of claim 1, wherein said differentiating agent is selected from the group consisting of neurotrophic factor 3, epidermal growth  
15 factor, insulin-like growth factor 1 and a platelet-derived growth factor.

20. The method of claim 1, wherein said population containing protected neuronal cells comprises at least 50% neuronal cells.

20 21. The method of claim 1, further comprising the step of

(c) transplanting cells comprising a nucleic acid molecule encoding a MEF2 polypeptide or an active fragment thereof into a patient to produce a cell  
25 population containing protected neuronal cells in said patient.

22. An isolated stem cell, comprising an exogenous nucleic acid molecule encoding a MEF2 polypeptide or an active fragment thereof.

23. The isolated stem cell of claim 22, comprising  
5 a nucleic acid molecule encoding a MEF2 polypeptide, or active fragment thereof, operatively linked to a heterologous regulatory element.

24. The isolated stem cell of claim 22, wherein said MEF2 polypeptide is a human MEF2 polypeptide.

10 25. The isolated stem cell of claim 22, wherein said MEF2 polypeptide is a MEF2C polypeptide.

26. The isolated stem cell of claim 22, wherein said MEF2 polypeptide is constitutively active.

15 27. The isolated stem cell of claim 26, wherein said MEF2 polypeptide is a constitutively active MEF2C polypeptide.

28. The isolated stem cell of claim 26, wherein said constitutively active MEF2 polypeptide is a MEF2/VP16 fusion protein.

20 29. The isolated stem cell of claim 26, wherein said constitutively active MEF2 polypeptide contains one or more serine/threonine to aspartic acid/glutamic acid substitutions in the MEF2 transactivation domain.

25 30. The isolated stem cell of claim 22, which is a human stem cell.

31. The isolated stem cell of claim 22, which is an embryonic stem cell.

32. The isolated embryonic stem cell of claim 31, which is a human embryonic stem cell.

5        33. The isolated human stem cell of claim 30, wherein said MEF2 polypeptide is human MEF2C.

34. The isolated human stem cell of claim 30, wherein said MEF2 polypeptide is constitutively active.

35. An isolated hematopoietic stem cell, comprising  
10 an exogenous nucleic acid molecule encoding a MEF2 polypeptide or an active fragment thereof.

36. The isolated hematopoietic stem cell of  
claim 35, comprising a nucleic acid molecule encoding a  
MEF2 polypeptide, or active fragment thereof, operatively  
15 linked to a heterologous regulatory element.

37. The isolated hematopoietic stem cell of  
claim 36, which is a human hematopoietic stem cell.

38. A method of identifying a protective or differentiation gene, comprising:

(a) isolating a first cell population;

(b) isolating a second cell population, wherein said  
5 second cell population has an altered level or activity  
of a MEF2 polypeptide as compared to said first cell  
population; and

(c) assaying for differential gene expression in  
said first cell population as compared to said second  
10 cell population,

whereby a gene differentially expressed in said  
second cell population as compared to said first cell  
population is identified as a protective or  
differentiation gene.

15 39. The method of claim 38, wherein said first cell  
population is a progenitor cell population, said second  
cell population is a neuronal cell population, and said  
differentially expressed gene is a neuronal  
differentiation gene.

20 40. The method of claim 38, wherein said first cell  
population is a progenitor cell population, said second  
cell population is a muscle cell population, and said  
differentially expressed gene is a muscle differentiation  
gene.

25 41. The method of claim 38, wherein said first and  
second cell populations are neuronal cell populations,  
said second cell population has been subject to a  
neuronal stress as compared to said first cell  
population, and said differentially expressed gene is a  
30 neuroprotective gene.

42. A method of identifying a protective gene *in vitro*, comprising the steps of:

(a) inducing the p38/MEF2 pathway in a cell *in vitro* to produce a protected cell;

5 (b) stressing said cell; and

(c) assaying for differential gene expression in said protected cell as compared to gene expression in a control cell,

whereby a gene differentially expressed in said  
10 protected cell as compared to said control cell is identified as a protective gene.

43. The method of claim 42, wherein step (a) comprises introducing into said cell a nucleic acid molecule encoding a MEF2 polypeptide.

15 44. The method of claim 42, wherein said MEF2 polypeptide is a human MEF2 polypeptide.

45. The method of claim 42, wherein said MEF2 polypeptide is a constitutively active MEF2 polypeptide.

20 46. The method of claim 42, wherein said cell is a neuron.

47. The method of claim 42, wherein said cell is a muscle cell.

48. The method of claim 42, wherein said differential gene expression is increased gene  
25 expression.

49. The method of claim 42, wherein said differential gene expression is decreased gene expression.

50. A method of identifying a differentiation gene  
5 *in vitro*, comprising the steps of:

- (a) inducing the p38/MEF2 pathway in a progenitor cell *in vitro* to produce a differentiated cell; and
- (b) assaying for differential gene expression in said differentiated cell as compared to gene expression  
10 in a control cell,

whereby a gene differentially expressed in said differentiated cell as compared to said control cell is identified as a differentiation gene.

51. The method of claim 50, wherein step (a)  
15 comprises introducing into said progenitor cell a nucleic acid molecule encoding a MEF2 polypeptide.

52. The method of claim 50, wherein said MEF2 polypeptide is a human MEF2 polypeptide.

53. The method of claim 50, wherein said MEF2  
20 polypeptide is a constitutively active MEF2 polypeptide.

54. The method of claim 50, wherein said differentiated cell is a neuronal cell.

55. The method of claim 50, wherein said differentiated cell is a muscle cell.



56. The method of claim 50, wherein said differential gene expression is increased gene expression.

57. The method of claim 50, wherein said  
5 differential gene expression is decreased gene expression.